

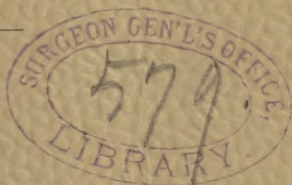
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REPORT OF A CASE OF ECTOPIC GESTATION ASSOCIATED WITH TUBERCULOSIS OF THE TUBES, PLACENTA, AND FETUS.

BY

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**REPORT OF A CASE OF ECTOPIC GESTATION
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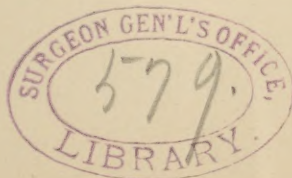
By ALFRED SCOTT WARTHIN, M.D.,
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IN so far as I have been able to discover, the case which I present in this report is unique in being the first case of extrauterine pregnancy associated with tuberculosis of the tubes, that has yet been observed. While the field of the etiology of ectopic gestation is thus enlarged by the admission of a new factor, the case becomes more important because of the undoubted proof of the existence of tuberculosis in the placenta and fetus. For this reason its relation to the question of the inheritance of tuberculosis gives the case the greatest scientific interest. This question, still open to discussion, receives here important evidence as to the possibility of the infection of the child from a diseased parent in its intrauterine life.

The patient who forms the subject of this report was from the clinic of Dr. James N. Martin, Professor of Gynecology and Obstetrics in the University of Michigan, and to his kindness and courtesy I am indebted for the history of the case and the results of the operation. The history is briefly as follows:

Mrs. F. C., thirty-eight years of age, had been married for thirteen years. She had had no children and no abortions. Her periods had always been regular until August, 1895. At that time she menstruated in the second week, and then did not have a return until February, 1896. From

¹ Read before the Michigan State Medical Association, June, 1896.



August to October she felt well, but early in that month she had a sudden attack of sharp and sickening pains low down in her left side. The patient described these pains as darting in all directions, and "feeling as if the navel was being pulled backward." There was a decided tendency to collapse, but the symptoms soon subsided. Two days after she had another, but less severe attack, and six days later she was again attacked with pains so severe that the use of morphin was necessary. After the attack the patient felt very weak and faint; a general peritonitis followed, and it was thought that there was an intestinal obstruction. From this attack she recovered slowly. Four weeks later she had sensations of throbbing, heat, and pain in the pelvis. This was followed by an abundant dark-brownish discharge from the vagina, containing soft, cheesy masses, looking like thick pus. Toward the end of each discharge an offensive odor was noticed. These discharges continued at intervals for about three weeks, being always preceded by sensations of throbbing, heat, and pain. At this time there was passed something resembling a small sack. From the beginning of the trouble the patient gradually declined and lost strength. She could not rest upon either side because of drawing sensations.

Her periods returned in February and again in March. These lasted but one day, the usual duration having been from one and a half to three days. The amount was small and there was much pain. She had also at times a thick white discharge from the vagina, small in amount.

She was admitted to the University Hospital on the 26th of March, 1896. Her general condition at this time was fair, there was a slight anemia; she was weak but not emaciated. Her appetite was fair, but digestion was not normal. The bowels were regular. Her locomotion was not difficult. There were no symptoms on the part of heart or lungs. During the week preceding the opera-

tion she had no temperature, and there was nothing in the general aspect of the case to suggest tuberculosis.

The physical examination was made on the 27th. The examination of the heart and lungs was negative. On the left side and low down close to the walls of the pelvis, there were dulness and some thickening. The vault of the vagina was tense. The cervix and uterus rested backward, the uterus being immovable, and very sensitive. It measured two and a half inches. At the left of the uterus, extending obliquely outward and upward toward the wall of the pelvis, there was an oval mass, rather irregular in outline and very sensitive. This pushed the uterus to the right, and the cervix somewhat backward. No examination of the blood was made. The urine examination was negative with the exception of the presence of a small amount of pus. Neither this nor the vaginal discharge was stained for tubercle bacilli.

With the exception of the cessation of the menses, the patient had had no symptoms or signs that would lead her to believe that she was pregnant, and she did not think that she was in that condition. The diagnosis of extrauterine pregnancy was, however, made by Dr. Martin, and the patient was prepared for operation. This took place on the 3d of April.

A median incision was made. The parts were found to be very vascular, and there were many adhesions between the uterus, appendages, and intestines. The right tube was found to be tortuous and enlarged, and the ovary cystic. These were removed and the stump cauterized. In the fimbriated extremity was a nodular hemorrhagic mass, about the size of a hazelnut. This was separated during the operation and preserved for future examination. The left ovary was found in about its normal location. It was enlarged and cystic. Above it, and attached to it by many adhesions, extended the thickened and twisted tube which passed upward into a mass about the

size of a cocoanut. This mass was covered by friable adhesions, and lay up well toward the intestines. The distal portion of the tube passed into the lower surface of this mass and was lost in the adhesions covering it. About an inch to the right of this the greatly thickened tube was again found and traced on to the uterus, the cyst, therefore, arose from the tube about an inch and a half from this organ. The mass was dissected out with the greatest difficulty. When the adhesions covering the upper surface were removed, the head of a fetus was seen protruding from a rent in this portion of the mass. In removing the cyst the distal portion of the tube, together with the ovary, was separated. These were also removed. The uterine portion of the tube was severed about one-half inch from the uterus, and the stump cauterized. The cyst was then opened in the presence of the class and the fetus demonstrated, but the tubercular nature of the tubal disease was not then suspected. After the demonstration, the specimens were placed in four per cent. solution of formalin and brought to my laboratory.

On the next morning I began my examination of these, with the following results:

Right ovary and tube.—The right ovary was about the size of a small walnut; its surface was slightly nodular. Between it and the tube there was a mass of new tissue, about one-fourth of an inch thick, nodular, and hemorrhagic. From this mass a piece attached to the fimbriae had been removed during the operation. The cut surface of the ovary showed the usual hyalin and cystic degeneration of the Graafian scars. The gross appearance of the small hemorrhagic mass was so characteristic of the hemorrhagic tubercles of the peritoneum, that it was at once cut and stained. The suspicion was confirmed by the microscopical picture. The mass consisted almost entirely of epithelioid cells; in some portions there was a reticulum of rather coarse connective-tissue fibers. There

were also large areas of caseous necrosis, and among the epithelioid cells at the periphery of the caseated areas there were occasional giant-cells with many nuclei. Many of these giant-cells showed beginning caseation. There were but few blood-vessels. Large areas showed extensive recent hemorrhages, while others gave evidence of old extravasation by the large amount of hemosiderin scattered throughout the tissue. Sections of this mass were stained for tubercle bacilli in the usual way, with carbolic fuchsin, and the presence of the bacilli in scanty numbers was demonstrated.

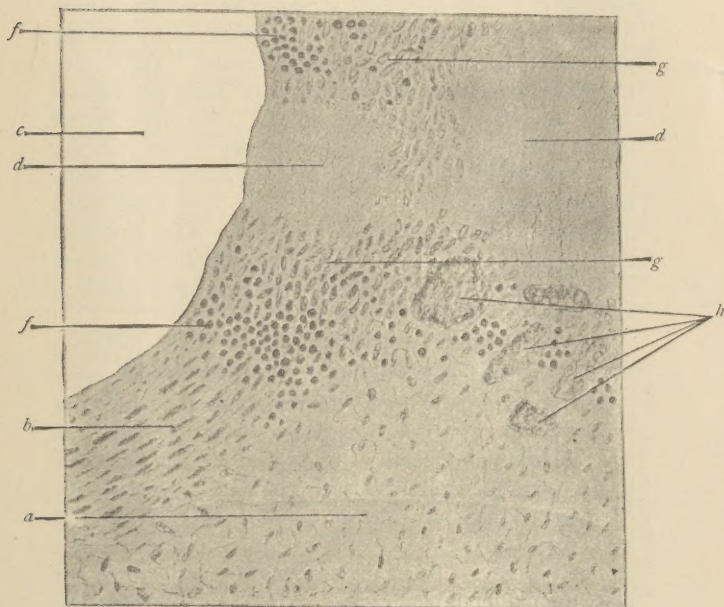
On cutting into the distended right tube it was found to be filled with a soft, cheesy substance, which had not been entirely hardened by the formalin. Smears were made from this and stained for tubercle bacilli, with negative results. Thin transverse sections of the tube were then hardened in absolute alcohol, embedded in celloidin and cut. Some of these sections were stained with the Van Gieson's stain, and others with hemalum. These sections, on examination, were found to give a beautiful picture of tubal tuberculosis. The wall of the tube was much thickened, the vessels were congested, and there were numerous areas of hemorrhage and small-celled infiltration in the connective tissue, and between the layers of muscle. Small miliary tubercles were also numerous throughout the wall and under the outer coat. In many sections the lumen of the tube was entirely filled by a mass of tubercles in all stages of growth, the epithelium of the plications of the mucosa being entirely lost. The tubercles were chiefly epithelioid, with a limited small-celled infiltration around the periphery. In some sections giant-cells were numerous, in others only a few could be found. Extensive areas of caseation with occasional masses of calcification were found in some sections. In others the lumen was only partly obstructed, and numerous small miliary tubercles were scattered through

the mucosa just beneath the epithelium, which was preserved. These tubercles were epithelioid, with a moderate small-celled infiltration. Giant-cells were numerous, but caseation was not extensive. Masses of calcification were not uncommon. In many places the folds of the mucosa presented a perfectly normal structure, except for the presence of the tubercles, but in others there was a marked inflammatory process with destruction of the mucosa, and the presence of large areas of small-celled infiltration. Some of these areas were freshly hemorrhagic, others were full of hemosiderin. Toward the uterine end of the tube the process became more miliary in type, and less marked. The sections of this tube stained for the bacilli gave negative results.

Left ovary.—The left ovary was much larger than the right, about the size of a large walnut. The surface was uneven and covered with the stringy remains of many adhesions which had bound it to the cyst. Many small cysts projected on its surface, and on its upper margin a true corpus luteum presented. The cut surface showed numerous small cysts, hyalin scars, and a true corpus luteum, about three-quarters of an inch in diameter, and of a pale yellow. The convoluted inner margin surrounded a mass of coagulated mucin which was slightly hemorrhagic. The fimbriated extremity of the tube was occluded by a small hemorrhagic mass, and in the fimbriæ were several small cysts and a few small, firm, yellowish nodules. The tube was much distended and twisted, but became about normal in size at the point where it passed into the cyst. On the surface of the tube and ovary there were several small, irregular, brownish masses attached loosely by thin bands of adhesions. Sections of these nodules showed them to be hemorrhagic tubercles of the same character as the one from the right ovary, having the same resemblance to the hemorrhagic tubercles so often found on the peritoneum.

Sections of the distal end of the tube, when examined microscopically, gave a picture similar to that of the right side. There was a miliary tuberculosis of the mucosa,

FIG. 1.



SECTION OF UMBILICAL CORD (ABOUT 175x).¹

a—Normal tissue of cord. *b*—Wall of umbilical vessel. *c*—Lumen of vessel. *d*—Areas of caseation. *f*—Small-celled infiltration. *g*—Epithelioid cells. *h*—Masses of calcification.

but in some sections the appearance was that of a diffuse process affecting also the walls of the tube. There were

¹ Made from formalin-hardened and celloidin-imbedded portion of cord, stained with Van Gieson's stain. Owing to the partial necrosis of the cord it was necessary to greatly over stain in order to bring out the nuclei, the tuberculous area, however, staining much more deeply than the tissue of the cord.

large areas of caseation and calcification. Sections from this part of the tube, stained for the tubercle bacilli, gave negative results. The portion of the tube between the uterus and the cyst was also twisted and greatly distended, especially at the point where it passed into the cyst where its diameter reached an inch. It was filled with yellowish material of the consistence of firm cheese. The microscopical examinations of sections taken from this portion of the tube showed a chronic diffuse tuberculosis rather than a miliary process. The lumen was almost entirely filled in some places by a reticulated tubercular mass containing numerous giant-cells; and there were many areas of caseation and calcification. Only a few of the epithelial folds remained preserved. In many places the process extended into the muscular coat, and quite large tubercles were occasionally found there.

Cyst.—The cyst consisted of an outer capsule inclosing the red, spongy, and irregular-shaped mass, which comprised the placenta and the fetal membranes. The outer surface of the cyst was rough, somewhat irregular, and covered with the remains of stringy adhesions. On cutting through the wall numerous yellow areas were found, of varying size, from that of a pin-head to that of a small finger-nail. Some of these were firm, others were soft and cheesy. These masses extended throughout the placenta and fetal membranes. In the cavity of the cyst lay a male fetus, flattened and somewhat macerated, about seven inches in length. Its age was evidently between three and four months, the finger-nails and the glans penis being formed, but the prepuce and scrotum not yet developed. The umbilical cord was about eight inches long, and arose from the lower part of the cyst, very near the large tubercular mass in the uterine portion of the tube.

Fetus.—At about three-fourths of the length of the cord, from its origin toward the fetus, there were several well-marked nodules, one containing yellowish caseous

material, the largest one quite firm, except in its center, which was soft and yellow. These were cut off for hardening and embedding. The fetus was also opened, and the liver, spleen, kidneys, and lungs, were removed and hardened. These organs were almost entirely necrosed, the liver consisting only of a reddish, cheesy mass, crumbling into bits. Some of the yellow areas in the cyst-wall and placenta were also prepared for examination. The microscopic examination of the sections taken from the cyst-wall showed it to be the greatly distended tube, as the thin layers of muscle could still be detected. The yellowish areas in the wall proved to be giant-celled epithelioid tubercles with calcification. The examination of the similar areas in the placenta showed them to be the same thing. Throughout the whole placental tissue typical tubercles could be found. In one section, stained for tubercle bacilli, their presence was demonstrated.

The tuberculous changes in the placenta could be separated into two groups according to their location, a villous and an intervillous form. In the first the earliest changes took place within the villus itself, the epithelioid cells arising from the connective-tissue cells of the villus, or possibly from the endothelial cells of the placental capillaries, though this could not be shown. Whatever the origin of the tubercle, it is certain that in its development the connective-tissue cells of the villi play the chief part in the production of the epithelioid cells. In those villi in which the process was in an early stage and confined to its inner portion the outer surface remained intact, but with the increased growth of the tubercle this was lost, and the epithelioid cells had broken through into the intervillous spaces. In its further growth the tubercular tissue completely filled these spaces, and in many cases extended around normal villi which stood out sharply against it. The intervillous tubercles were far more abundant than those originating primarily in the villi. In these the first

change observed was a proliferation of cells on the surface of the villus at a point where the outer layer of cells could no

FIG. 2.



TUBERCULOSIS OF PLACENTA (170x).¹

a—Epithelioid cells. *b*—Giant-cells. *c*—Areas of caseation. *d*—Small-cell infiltration. *e*—Masses of calcification. *f*—Fibrin. *g*—Placental villi (Most of these show mucous degeneration and calcification). *h*—Red blood-corpuscles.

longer be seen. The connective tissue of the villus, however, presented no change. It is probable that here the

¹ From portion of placenta hardened in formalin and alcohol; cut in celloidin and stained with hematoxylin.

epithelioid cells arose from a proliferation of the cells covering the villi. The growth of the tubercle is then outward into the blood-spaces and consists of a proliferation of its own epithelioid cells. This growth, in many cases, was very extensive, filling in completely the spaces between many villi and entirely surrounding them. In many cases prolongations of epithelioid cells could be seen extending out into the masses of fibrin which filled many of the blood-spaces. The areas of caseation were in those parts of the new tissue farthest away from the circulating blood, and, as a rule, the giant-cells lay in the central portions of the mass, and not at the periphery. In some cases the tubercular growth seemed to extend inward into the tissue of the villi as well as out into the blood-spaces. The majority of the villi primarily affected, as well as those surrounded by tubercular tissue, showed more or less degeneration. In many of them the entire outer layer of cells was lost, the connective-tissue nuclei stained very faintly, and there was mucous or fatty change with large masses of calcification. These changes are all shown in the drawing in which the intervillous form is reproduced.

As to the manner of infection of the placenta, it seems very probable that the bacilli set free from the diseased maternal structures of the tube came with the maternal blood into the intervillous spaces. Here they were deposited upon the surfaces of the villi of the fetal placenta and set up their characteristic changes. As to the primary tubercles in the villi the origin is not so clear. It may, however, be supposed that their production may be due to an entrance of bacilli into the circulation of the villi, and hence into the fetal vessels, at those points where the epithelioid cells have grown into the villus from its surface; and with the caseation and breaking down of the new tissue the bacilli have been set free into the capillaries of the villi, and so could pass into the circulation of the fetus. Since it is definitely shown that the placental tissue has no

immunity against tuberculosis, there is no reason to believe that the spread of the process through it would differ in any way from that in any other part of the body.

The sections from the nodules in the cord showed, near the necrosed wall of a large vessel, a loosely reticulated tissue of epithelioid cells and small-celled infiltration. No giant-cells were found, but the character of the tissue with areas of caseation marked it as undoubtedly tubercular. The microscopical examination of the internal organs was negative. The liver consisted almost entirely of formless dead matter. Hundreds of sections of this were stained for the bacilli with negative results. It is greatly to be regretted that we did not recognize the existence of tuberculosis before the specimens were put into the formalin, as the presence of bacilli in the internal organs might have been shown by injecting animals with portions of the organs, or by making cultures from them. Only in the lung was anything like a tubercle found. On cutting this organ, after hardening preparatory to imbedding, two whitish areas about the size of small pin-heads were seen. On section these proved to be two small areas of complete necrosis where the structure was lost, while the tissue about showed faintly staining nuclei without this loss of form. These were, therefore, very highly suggestive of miliary tubercles, but the fact could not be positively decided. One of my assistants thought that he discovered tubercle bacilli in a section of the kidney stained for these, but when I went to look at them they could not be found. Therefore, so far as the fetus is concerned, the actual demonstration in its structures of tubercular changes must be confined to the membranes and cord, but it seems almost certain that the internal organs must have been similarly affected, though this could not be demonstrated beyond all doubt.

The patient died of general peritonitis on the 13th of April, ten days after the operation. An autopsy was re-

fused, so the existence of tuberculosis in the other organs could not be ascertained. As mentioned before, there were no signs or symptoms which would lead us to suspect any other localization of the disease, so that I think the case may be looked upon as a primary tuberculosis of the genital tract. From a sister of the patient it was learned that a year and a half ago the latter's husband had been ill with fever, night-sweats, general weakness, and loss of flesh, and was on this account thought to have consumption, but he afterward entirely recovered. The family physician, in answer to my letter of inquiry, informed me that the husband is now perfectly well, without signs or symptoms of tuberculosis. Specimens of his urine, which were sent to me for examination for tubercle bacilli, have not arrived, so I have been unable to throw any definite light upon the etiology of the patient's condition, or to establish any relation between it and her husband's symptoms of a year and a half ago.

In conclusion, tuberculosis of the tubes, it seems to me from this case, must be considered as an etiological factor in the production of ectopic gestation. If the obstruction of the tube hindering the progress of the ovum toward the uterus is the chief factor, we have in the almost complete obliteration of the canal by the numerous miliary tubercles in the mucosa, a most favorable condition for its occurrence. It is very probable that the salpingitis which is found to exist in almost every case of extrauterine pregnancy, and which is usually looked upon as the causal factor, may, in more cases than is now suspected, be found to be tuberculous.

Up to a very short time ago, tuberculosis of the female genital tract, though it had been known to exist for a long period of time, did not assume that importance which it is now beginning to hold. During the last three years it has been shown that far from being a rare disease, it occurs in a very large proportion of all the cases treated

for inflammatory disease of this tract. Williams, of Johns Hopkins, in a very exhaustive article in the "Johns Hopkins Hospital Reports for 1892," reviews the subject up to that year. He makes the statement that in his own experience, about eight per cent. of all the cases in which the appendages are removed for inflammatory disease are tubercular; in other words, every twelfth case of adherent tubes and ovaries, or pus-tubes, is of tubercular origin. He further emphasizes the difficulty of making a microscopic diagnosis. Of his cases only twenty-five per cent. were suspected tuberculosis, seventy-five per cent. being unsuspected as far as this condition was concerned. Since the ultimate diagnosis is, therefore, a microscopical one, it is very probable that a wider experience in making these examinations will increase greatly the proportion in which it is found to occur. The importance, on this account, of a technical examination, as a matter of routine, in all of the cases of tubal inflammation, cannot be too strongly urged.

Tuberculosis of the ovary is not so common as that of the tubes, but still occurs so frequently that it cannot be looked upon as a rare condition. It is most frequently met with on the surface of the organ, but Williams and numerous other observers have found it in the body of the ovary, even in the walls of cystic tumors. With it there is usually found a tuberculosis of the tubes or uterus. In our own case the small nodules attached to the surface of the ovary are really tubercles of the peritoneum. It is here worthy of note that tuberculosis of the tubes must be looked upon as perhaps the most important factor of infection in tubercular peritonitis. It is due largely to the fact that laparotomy has lately been so extensively adopted as a cure for this condition that the occurrence of tubercular salpingitis has been discovered to be of so frequent occurrence, since in the majority of cases the conditions have been found to be coexistent. The small nodules that were found in this case may, I think, be looked upon

as an early stage of tubercular peritonitis in which the infection undoubtedly arose from a diseased tube. The location of the tubercles upon the surface of the ovary and in the fimbriated extremity all point strongly to this mode of origin. It should be mentioned here, however, that some authorities believe the tubal disease to be always secondary to that of the peritoneum, the tube taking in the bacilli from the peritoneal cavity.

Up to the date of Williams' article in 1892, only one case of tuberculosis of the placenta had been reported, and from the description given of that case its nature is somewhat doubtful. But F. Lehmann, in 1893 (*Deutsch. med. Wochenschr.*, 1893), found typical tubercles in the placenta of a woman dying from acute miliary tuberculosis in the seventh or eighth month of pregnancy. Schmorl and Kockel, in 1894 (*Beiträge v. Seigler*, xvi, 1894), also made a report upon this condition, so that this is the third instance in which placental tuberculosis has been reported. Schmorl, Birch-Hirschfeld, and Landouzy, had, however, demonstrated the presence of the tubercle bacilli in the blood of the placenta and of the fetal organs, and were able to make cultures and successful inoculations with material from these organs. Histological changes were not definitely ascertained by these investigators.

The presence of the tubercles in the umbilical cord makes the case important, because it is the first one reported in which that condition has been found. This gives added evidence to the still-mooted questions of the inheritance in the child of tuberculosis from the mother. I regret deeply that I could not satisfy myself as to the presence of tubercle bacilli in the internal organs of the fetus, as it seems almost certain that they must be present.

The cases mentioned above, in which the presence of the bacilli was demonstrated in the fetus, were all cases of acute miliary tuberculosis, the mother dying in pregnancy. It seems very improbable that infection of the

fetus in this disease can play much part in the inheritance of tuberculosis because of the death of parent and child before birth occurs. It would be more important to prove the possibility of infection from a localized tuberculosis of the tubes or uterus in which condition the fetus might go to full term and delivery, and so come infected into the world. This case, I think, goes very far toward proving the possibility of this event.

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